

## Abstract

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### ESHRE guideline: ovarian stimulation for IVF/ICSI

Ernesto Bosch<sup>1</sup>, Simone Broer<sup>2</sup>, Georg Griesinger<sup>3</sup>, Michael Grynberg<sup>4</sup>

<sup>1</sup>*IVI-RMS Valencia, Valencia, Spain.*

<sup>2</sup>*Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands.*

**Study question:** What is the recommended management of ovarian stimulation, based on the best available evidence in the literature?

**Summary answer:** The guideline development group formulated 84 recommendations answering 18 key questions on ovarian stimulation.

**What is known already:** Ovarian stimulation for IVF/ICSI has been discussed briefly in the National Institute for Health and Care Excellence guideline on fertility problems, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologist has published a statement on ovarian stimulation in assisted reproduction. There are, to our knowledge, no evidence-based guidelines dedicated to the process of ovarian stimulation.

**Study design size duration:** The guideline was developed according to the structured methodology for development of ESHRE guidelines. After formulation of key questions by a group of experts, literature searches and assessments were performed. Papers published up to 8 November 2018 and written in English were included. The critical outcomes for this guideline were efficacy in terms of cumulative live birth rate per started cycle or live birth rate per started cycle, as well as safety in terms of the rate of occurrence of moderate and/or severe ovarian hyperstimulation syndrome (OHSS).

**Participants/materials setting methods:** Based on the collected evidence, recommendations were formulated and discussed until consensus was reached within the guideline group. A stakeholder review was organized after finalization of the draft. The final version was approved by the guideline group and the ESHRE Executive Committee.

**Main results and the role of chance:** The guideline provides 84 recommendations: 7 recommendations on pre-stimulation management, 40 recommendations on LH suppression and gonadotrophin stimulation, 11

recommendations on monitoring during ovarian stimulation, 18 recommendations on triggering of final oocyte maturation and luteal support and 8 recommendations on the prevention of OHSS. These include 61 evidence-based recommendations-of which only 21 were formulated as strong recommendations-and 19 good practice points and 4 research-only recommendations. The guideline includes a strong recommendation for the use of either antral follicle count or anti-Müllerian hormone (instead of other ovarian reserve tests) to predict high and poor response to ovarian stimulation. The guideline also includes a strong recommendation for the use of the GnRH antagonist protocol over the GnRH agonist protocols in the general IVF/ICSI population, based on the comparable efficacy and higher safety. For predicted poor responders, GnRH antagonists and GnRH agonists are equally recommended. With regards to hormone pre-treatment and other adjuvant treatments (metformin, growth hormone (GH), testosterone, dehydroepiandrosterone, aspirin and sildenafil), the guideline group concluded that none are recommended for increasing efficacy or safety.

**Keywords:** ESHRE; GRADE; evidence based; guideline; high responder; ovarian hyperstimulation syndrome; ovarian stimulation; poor responder; treatment.

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### Magnetic resonance-high intensity focused ultrasound (MR-HIFU) therapy of symptomatic uterine fibroids with unrestrictive treatment protocols: A systematic review and meta-analysis

Inez M Verpalen<sup>1</sup>, Kimberley J Anneveldt<sup>2</sup>, Ingrid M Nijholt<sup>3</sup>

<sup>1</sup>*Department of Radiology, Isala hospital, Zwolle, the Netherlands. Electronic*

<sup>2</sup>*Department of Obstetrics and Gynecology, Isala hospital, Zwolle, the Netherlands.*

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**Purpose:** Reevaluation of the effectiveness of Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU) therapy for uterine fibroids by excluding studies with restrictive treatment protocols that are no longer used.

**Methods:** The National Guideline Clearinghouse, Cochrane Library, TRIP, MEDLINE, EMBASE and WHO International Clinical Trials Registry Platform (ICTRP) databases were searched from inception until the 22nd of June 2018. Keywords included “MR-HIFU”, “MRgFUS”, and “Leiomyoma”. Only studies about MR-HIFU treatment of uterine fibroids with at least three months of clinical follow-up were evaluated for inclusion. Treatments with ultrasound-guided HIFU devices or protocols not aiming for complete ablation were eliminated. The primary outcome was the improvement in fibroid-related symptoms. Technical outcomes included screening and treatment failures, treatment time, application of bowel-interference mitigation strategies and the Non-Perfused Volume (NPV) percentage. Other secondary outcomes were the quality of life, fibroid shrinkage, safety, re-interventions, reproductive outcomes, and costs. Meta-analysis was performed using a random-effects model (DerSimonian and Laird).

**Results:** A total of 18 articles (1323 treated patients) met the inclusion criteria. All selected studies were case series except for one cross-over trial. Overall, the quality of the evidence was poor to moderate. The mean NPV% directly post-treatment was 68.1%. The use of bowel-interference mitigation strategies may lead to increased NPV%. The mean symptom reduction at 12-months was 59.9% and fibroid shrinkage was 37.7%. The number of adverse events was low (8.7%), stratification showed a difference between HIFU systems. The re-intervention percentage at 3-33.6 months follow-up ranged from 0 to 21%. Longer follow-up was associated with a higher risk at re-interventions. Reproductive outcomes and costs couldn't be analyzed.

**Conclusions:** Treatment guidelines aiming for complete ablation enhanced the effectiveness of MR-HIFU therapy. However, controlled trials should define the role of MR-HIFU in the management of uterine fibroids.

**Keywords:** High-intensity focused ultrasound ablation; MR guided interventional procedures; Systematic review; Uterine fibroids.

### **New advances in ovarian autotransplantation to restore fertility in cancer patients**

Mahmoud Salama<sup>1</sup> and Teresa K. Woodruff<sup>2</sup>

Human ovary autotransplantation is a promising option for fertility preservation of young women and girls undergoing gonadotoxic treatments for cancer or

some autoimmune diseases. Although experimental, it resulted in at least 42 healthy babies worldwide. According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic literature review was performed for all relevant full-text articles published in English from 1 January 2000 to 01 October 2015 in PubMed to explore the latest clinical and research advances of human ovary autotransplantation. Human ovary autotransplantation involves ovarian tissue extraction, freezing/thawing, and transplantation back into the same patient. Three major forms of human ovary autotransplantation exist including (a) transplantation of cortical ovarian tissue, (b) transplantation of whole ovary, and (c) transplantation of ovarian follicles (artificial ovary). According to the recent guidelines, human ovary autotransplantation is still considered experimental; however, it has unique advantages in comparison to other options of female fertility preservation. Human ovary autotransplantation (i) does not need prior ovarian stimulation, (ii) allows immediate initiation of cancer therapy, (iii) can restore both endocrine and reproductive ovarian functions, and (iv) may be the only fertility preservation option suitable for prepubertal girls or for young women with estrogen-sensitive malignancies. As any other fertility preservation option, human ovary autotransplantation has both advantages and disadvantages and may not be feasible for all cases. The major challenges facing this option are how to avoid the risk of reintroducing malignant cells and how to prolong the lifespan of ovarian transplant as well as how to improve artificial ovary results.

**Keywords:** Ovary autotransplantation, Female fertility preservation, Cancer, Cryopreservation, *In vitro* maturation, Oncofertility

### **Pregnancy-related complications and perinatal outcomes resulting from transfer of cryopreserved versus fresh embryos in vitro fertilization: a meta-analysis**

Tingting Sha<sup>1</sup>, Xunqiang Yin<sup>2</sup>, Wenwei Cheng<sup>3</sup>, Isaac Yaw Massey<sup>4</sup>

<sup>1</sup>Department of Epidemiology and Medical Statistics, Xiangya School of Public Health, Central South University, Hunan, People's Republic of China.

<sup>2</sup>Department of Maternal and Child Health, Xiangya School of Public Health, Central South University, Hunan, People's Republic of China. *Electronic*

**Objective:** To provide an updated comparison of pregnancy-related complications and adverse

perinatal outcomes of pregnancies conceived after frozen embryo transfer (FET) versus fresh embryo transfer (fresh ET).

**Design:** Meta-analysis.

**Setting:** University.

**Patient(s):** Pregnancies resulting from FET versus fresh ET.

**Interventions(s):** Pubmed, Embase, Cochrane Library, Google Scholar, and Chinese databases, including the China National Knowledge Infrastructure Database, Wanfang, and Chinese Scientific Journals Full-Text Database were searched by two independent reviewers from January 1980 to September 2017. The results were expressed as risk ratios with 95% confidence intervals.

**Main outcome measure(s):** Pregnancy-related complications and perinatal outcomes.

**Result(s):** Our search retrieved 1,397 articles, of which 31 studies were included. Pregnancies resulting from FET were associated with lower relative risks of placenta previa, placental abruption, low birth weight, very low birth weight, very preterm birth, small for gestational age, and perinatal mortality compared with fresh ET. Pregnancies occurring from FET were associated with increased risks of pregnancy-induced hypertension, postpartum hemorrhage, and large for gestational age compared with fresh ET. The risks of gestational diabetes mellitus, preterm premature rupture of the membranes, and preterm birth (PTB) showed no differences between the two groups.

**Conclusion(s):** Our analysis demonstrated that FET results in lower risks of placenta previa, placental abruption, low birth weight, very low birth weight, very preterm birth, small for gestational age, and perinatal mortality than fresh ET, some differences that are attributed to the increased risks of pregnancy-induced hypertension, large for gestational age, and postpartum hemorrhage. Although cryotechnology keeps improving, for comprehensive consideration, individual approaches remain appropriate to balance the options of FET or fresh ET at present.

**Keywords:** Embryo transfer; in vitro fertilization; perinatal outcome; pregnancy complications.

## **Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome**

Helena J Teede,<sup>1</sup> Marie L Misso,<sup>2</sup> Michael F Costello,<sup>3</sup> Anuja Dokras,<sup>4</sup>

**Study Question:** What is the recommended assessment and management of women with polycystic ovary syndrome (PCOS), based on the best available evidence, clinical expertise and consumer preference?

**Summary Answer:** International evidence-based guidelines, including 166 recommendations and practice points, addressed prioritized questions to promote consistent, evidence-based care and improve the experience and health outcomes of women with PCOS.

**What is Known Already:** Previous guidelines either lacked rigorous evidence-based processes, did not engage consumer and international multidisciplinary perspectives, or were outdated. Diagnosis of PCOS remains controversial, and assessment and management are inconsistent. The needs of women with PCOS are not being adequately met and evidence practice gaps persist.

**Study Design, Size, Duration:** International evidence-based guideline development engaged professional societies and consumer organizations with multidisciplinary experts and women with PCOS directly involved at all stages. Appraisal of Guidelines for Research and Evaluation (AGREE) II-compliant processes were followed, with extensive evidence synthesis. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was applied across evidence quality, feasibility, acceptability, cost, implementation and ultimately recommendation strength.

**Participants/Materials, Setting, Methods:** Governance included a six continent international advisory and a project board, five guideline development groups, and consumer and translation committees. Extensive health professional and consumer engagement informed guideline scope and priorities. Engaged international society-nominated panels included pediatrics, endocrinology, gynecology, primary care, reproductive endocrinology, obstetrics, psychiatry, psychology, dietetics, exercise physiology, public health and other experts, alongside consumers, project management,

evidence synthesis and translation experts. In total, 37 societies and organizations covering 71 countries engaged in the process. Twenty face-to-face meetings over 15 months addressed 60 prioritized clinical questions involving 40 systematic and 20 narrative reviews. Evidence-based recommendations were developed and approved via consensus voting within the five guideline panels, modified based on international feedback and peer review, with final recommendations approved across all panels.

**Main Results and the Role of Chance:** The evidence in the assessment and management of PCOS is generally of low to moderate quality. The guideline provides 31 evidence based recommendations, 59 clinical consensus recommendations and 76 clinical practice points all related to assessment and management of PCOS. Key changes in this guideline include: (i) considerable refinement of individual diagnostic criteria with a focus on improving accuracy of diagnosis; (ii) reducing unnecessary testing; (iii) increasing focus on education, lifestyle modification, emotional wellbeing and quality of life; and (iv) emphasizing evidence based medical therapy and cheaper and safer fertility management.

#### **Risk of occult atypical hyperplasia or cancer in women with nonatypical endometrial hyperplasia**

Nara Lee Kwang Beom Lee Kidong Kim Jin Hwa Hong Ga Won Yim Seok Ju Seong Banghyun Lee Jong Min Lee Jaehyun Cho Soyi Lim Yung Taek Ouh Yong Beom Kim

**Objectives:** The aim of this study was to identify subsets of patients diagnosed with nonatypical endometrial hyperplasia (NAEH) by endometrial biopsy who had high risk for occult atypical endometrial hyperplasia (AEH) or endometrial cancer (EC).

**Methods:** We retrospectively reviewed the medical records of 281 patients who underwent hysterectomy within 6 months after a diagnosis of NAEH. We collected data on age, body mass index, menopausal status, tamoxifen use, previous history of NAEH, details of endometrial biopsy (location, curettage vs. pipelle sampling), NAEH subtype (simple vs. complex), interval between endometrial biopsy and hysterectomy, indication of hysterectomy and the presence of occult AEH or EC in hysterectomy specimen. Associations between variables and occult AEH or EC were analyzed. Risk of occult AEH or EC in subsets were calculated and visualized using a heatmap. **Results:** Among 281 patients, 34 (12.1%) and 9 (3.2%) had occult AEH and EC in hysterectomy specimens, respectively. Using univariate analysis, we found age, menopausal status and subtype were associated with occult AEH or EC. Using multivariate analysis, older age (odds ratio = 1.09,  $P < 0.01$ ) and complex subtype (odds ratio = 3.34,  $P < 0.01$ ) were independent risk factors. Patients at an age  $\geq 51$  years with complex NAEH had about 50% risk of occult AEH or EC.

**Conclusion:** Women at an age  $\geq 51$  years with complex NAEH had high risk for occult AEH or EC and surgical treatment can be considered for these patients.